UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,627	10/08/2003	Carl H. June		7408

7590 04/13/2010

U.S.A. REPRESENTED BY THE SECRETARY OF THE CHIEF
OF NAVAL RESEARCH ATTN: CHARLES SCHLAGEL
NAVAL MEDICAL RESEARCH CENTER
503 GRANT AVENUE
SILVER SPRING, MD 20910

EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
04/13/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,627	JUNE, CARL H.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-14,48 and 49* is/are pending in the application.

4a) Of the above claim(s) *10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-9,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08-07-2008 has been entered.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Status of Claims. Claims 1, 7-14, 48 and 49 are currently pending. Claim 1 has been amended, claims 3, 15, 17-19, 21, 22-45 have been canceled and claims 48 and 49 have been added by applicants amendment filed on 02-11-2010. Claims 10-14 were previously withdrawn form consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claims.
4. Therefore, claims 1, 7-9 and 48-49 are currently under examination to which the following grounds of rejection are applicable.

Response to Applicants' arguments

Rejoinder

At page 4 of the remarks filed on 02-11-2010, Applicants point that claim 7 is a generic claim that links Groups I, II and III. Applicants request rejoinder of withdrawn claims 10-14. Such is not persuasive.

The examiner notes that that because the claim 7 is not allowable as originally claimed, no other groups will be rejoined for search and examination at point of prosecution.

Withdrawn rejection in response to Applicants' arguments or amendments:

Claim Rejections - 35 USC § 102(e)

I view of Applicants' amendment of claim 1, rejection of claim 1 under 35 U.S.C. 102(e) as being anticipated by Bonjouklian et al., (U.S. Patent No. 5,504,103, Date of Publication, April 2 1996) has been withdrawn.

Though Bonjouklian et al., discloses methods of treating phosphatidylnositos-3-kinase dependent conditions in a mammal especially neoplasms, Bonjouklian et al., does not disclose treating rheumatoid arthritis or allergy.

Applicants' arguments are moot in view of the withdrawn rejection.

Rejections/objections maintained in response to Applicants' arguments or amendments:

Claim Rejections - 35 USC § 112 - enablement

To the extent that claims 1 and 48 broadly embrace an *in vivo* method of treating a human subject suffering from rheumatoid arthritis or allergy comprising contacting the T cell with an agent that inhibits rheumatoid arthritis (RA) or allergy the following rejection applies.

Note that the scope of enablement has been broaden in view of Applicants' remarks, in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art at the time of filing the present application and further in view of reconsideration of search under different premises.

Claim 1 remains rejected and claims 48 and 49 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for:

> A method for inhibiting T cell activation in a subject wherein the subject suffers from rheumatoid arthritis or allergy comprising contacting T cells with an agent which inhibits phosphatidylinositol 3-kinase activity in the T cells, wherein the agent is not a wortmannin, wherein the agent inhibits IL-2 production *in vitro* when said agent is applied to T cells that are stimulated by B-7-1 or B7-2, thereby inhibiting T cell activation in the subject suffering from rheumatoid arthritis or allergy,

does not reasonably provide enablement for claims directed to an *in vivo* method of treating a human subject suffering from allergies (e.g., asthma, rhinitis, anaphylaxis) or rheumatoid arthritis comprising merely contacting the T cell with an agent that inhibits phosphatidylinositol 3-kinase in T cells, wherein the contacting inhibits production of IL-2.

While applicants' amendment of claims 1 partially overcome some of the issues, some additional issues remain that are discussed below. A large embodiment of the instant application is to a method of treating allergy or rheumatoid arthritis in a subject by contacting T cells with an agent which inhibits phosphatidylinositol 3-kinase activity in the T cells. Issues related to the inhibition of phosphatidylinositol 3-kinase activity in the T cells in cells that have not been stimulated by B-7-1 or B7-2 have to be considered regarding the patentability of the broadly claimed methods. While the specification clearly exemplifies the percent inhibition by wortmannin (1 to 100 nM) of IL-2 production by human T cells stimulated with anti-CD3 antibody (OKT3) together with CHO cells expressing B7-1, B7-2 or both B7-1 and B7-2, the specification as filed is silent about the pathway of an inhibitor of phosphatidylinositol 3-kinase on production of interleukin-2 by T cells other than a CD28-dependent pathway. Indeed, Figure

7B clearly evidences the fact that IL-2 production stimulated by PMA in T cell by a pathway that is independent of CD28-stimulation is not inhibited or reduced by an inhibitor of phosphatidylinositol 3-kinase, e.g., wortmannin. The art at the time the invention was made teaches that T-cell antigen CD28 provides a signal that can synergize with T-cell antigen receptor stimulation in activating T cells to proliferate and secrete lymphokines, e.g., IL-2 (Harding et al., 1992, Nature, pp. 607-609; Johnson et al., 1993, *Immunol Res* 48-64; Abstract). Applicant has not provided sufficient guidance as to how to inhibit T cell activation by an agent which inhibits phosphatidylinositol 3-kinase activity without stimulation of T cells by CD28 ligand. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Of note, allergy (e.g., asthma, rhinitis, anaphylaxis) and rheumatoid arthritis are cell-mediated inflammatory reactions where it is desirable to downmodulate an immune response by inhibiting T cell activation (Mosmann et al., Immunology Today, pp.138-146; page 141, Table 2).

Rejection, Obviousness Type Double Patenting-

Claims 1 and 7-9 remain rejected and new claim 48 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789 for the reasons already of record as set forth in the office action of 12-12-2008.

Response to Applicant Arguments as they apply to rejection of Claims 1, 7-9 and 48 under nonstatutory obviousness-type double patenting

Applicants argue that the U.S. Patent No. 6, 632, 789 contain patentably distinct elements that are not present in the acclaims as curtly amended on the instant application. Such is not persuasive.

Claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789 are drawn to *in vivo* method of inhibiting the response by a T cell expressing a CD28 surface receptor which binds a costimulatory molecule comprising contacting the T cell with inhibitors of phosphatidylinositol 3-kinase such as quercetin and LY294002 and derivatives or analogs thereof. Because claims 1, 7-9 and 48 of the instant application are broadly drawn to any agent which inhibits production of phosphatidylinositol 3-kinase, claims 1, 7-9 and 48 embrace claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789, which claim quercetin and LY294002 as the specific inhibitory agents of phosphatidylinositol 3-kinase. Thus claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789, are species of the claimed genus in the instant invention and anticipate the claimed genus of agents that inhibits production of D-3 phosphoinositides.

New grounds of rejection

Claim Rejections - 35 USC § 103

To the extent that the claimed invention embraces methods for inhibiting T cell activation in a subject in need of wherein the subject suffers from rheumatoid arthritis or allergy comprising contacting the T cells with a phosphatidylinositol 3-kinase (PI3K) inhibitor that inhibits PI3K in the T cell, the following rejection applies, thereby inhibiting T cell activation in said subject, the following rejection applies.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over by Bonjouklian ET al., (U.S. Patent No. 5,504,103, Date of Publication, April 2 1996) in view of Vitali et al., (Int J Artif Organs. 1993 Dec;16 Suppl 5:196-200) or Bochner et al., (1994, *Ann. Rev Immunology,* pp. 295-335).

Note that new claim 49 is not included in the rejection. Though Bonjouklian teaches *in vitro* testing of β-hydroxywortmannin on bovine brain purified PI 3-kinase resulting on IC_{50} of 0.2 ng/ml (0.46 nM) (col. 11, lines 65-66 bridging to col. 12, lines 1-5), Bonjouklian does not disclose *in vitro* inhibition of IL-2 in T cell expressing a CD28 cell surface receptor and stimulated by its natural ligands B7-1(CD80) and B7-2 (B70).

Bonjouklian et al., teach methods of treating phosphatidylnositos-3-kinase dependent conditions in a mammal comprising contacting the cell with wortmannin or wortmannin analog (col. 14-16, claims 1-20). While Bonjouklian et al., teach the exact same method step as the instant claims (i.e. contacting cells with wortmannin), Bonjouklian et al., do not expressly teach

contacting T cells or specifically T cells which express a CD28 receptor with wortmannin. Bonjouklian et al., also do not expressly teach the modulation of T cell proliferation or modulation of lymphokine production. However, it is implicitly in the methods taught by Bonjouklian et al., that the administration of wortmannin or wortmannin analogs to a mammal results in the inhibition of phosphatidylinositol 3-kinase in any and all cells in mammals which express phosphatidylinositol 3-kinase. T cells are abundantly present in mammals and inherently express phosphatidylinositol 3-kinase. This finding is supported by the applicant disclosure in Figures 3, 4, 7a and 7b that contacting CD28 positive T cells with wortmannin results in inhibition of phosphatidylinositol 3-kinase. Thus, as it is clear that if T cells express phosphatidylinositol 3-kinase, it is implicitly in the method of inhibiting phosphatidylinositol 3-kinase in the cells in a mammal *in vivo* as taught by Bonjouklian et al., that phosphatidylinositol 3-kinase is inhibited in T cells present in that mammal. Furthermore, Bonjouklian et al., disclose treatment of pain, diabetes, inflammation, platelet aggregation, vascular diseases such as atherosclerosis, restenosis, and the like, and, particularly, abnormal cell growth as found in neoplasms (col. 6, lines 5-10).

Bonjouklian et al., does not specifically teach treatment of rheumatoid arthritis or allergy.

However, at the time the invention was made, Vitali et al., is an exemplified prior art that teaches that it is routine or well-established in the art to treat rheumatoid arthritis (RA) with immunosuppressive drugs that inhibit activation of the CD4+ T cell, and consequently of the cytokine network, which is the second step in the inflammatory process (Abstract). Likewise, Bochner is an exemplified prior art that teaches that it is routine or well-established in the art to

treat allergic conditions such as asthma with antagonist of pro inflammatory cytokines (Abstract).

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made, on teachings provided by the combined cited references, to treat a patient suffering from RA or allergy with an agent that inhibits phosphatidylinositol 3-kinase in T cells, particularly because Bonjouklian teaches that administration of wortmannin or wortmannin analogs to a mammal results in the inhibition of phosphatidylinositol 3-kinase thereby treating inflammation. Moreover, Vitali and Bochner evidence that reduction or inhibition of cytokines activity reduces the inflammatory process and anti inflammatory compounds are used in the treatment of RA and allergic asthma. All the claimed elements were known in the art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art of inhibiting T cell activation by inhibiting phosphatidylinositol 3-kinase activity in a subject suffering from rheumatoid arthritis or allergy.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

35 USC § 112- First paragraph- New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claim 49 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 49 recites "when less than about 100 nM of said agent is applied to T cells" . The specification discloses in FIG. 7B the percent inhibition by wortmannin at concentration of 1 to 100 nM of IL-production by human T cells stimulated for 24 hours with anti-CD3 antibody (OKT3) together with CHO cells expressing B7-1, B7-2 or both B7-1 and B7-2. Thus the specific embodiments regarding the breadth of "IL-2 production *in vitro* by at least 50% when less than about I00 nM of said agent is applied to T cells" sets forth a new range not previously disclosed as a contemplated embodiment in the present specification, nor one that was readily known and used in the art at the time of filing. Thus is not clear that the Applicant was in possession of a genus of undefined of "IL-2 production ... when less than about 100 nM of said agent is applied to T cells" including any open ended numerical range at the time the application was filed.

Conclusion

Claims 1, 7-9, 48 and 49 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633